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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/943,144	10/03/97	KOSHIBA T	21850208P-SP

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EXAMINER	
ZAGHMOUNT,O	

ART UNIT	PAPER NUMBER
1649	4

DATE MAILED: 03/17/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/943,144	Koshiba
Examiner	**Group Art Unit**
Ousama Zaghmout	1649

☒ Responsive to communication(s) filed on *Application was filed on: 10/03/97*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-16* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-16* is/are rejected.

☒ Claim(s) *4-7* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Status of application

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1649.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

This application does not contain the nucleotide sequence for inserted gene shown in Figure 1 of the specification (Please see attached notice for complying with requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures).

In the interest of compact prosecution, two time periods for the response are set to run concurrently: One month for compliance with the sequence rules, and the usual three months shortened statutory time period for the response to the first office action.

Claim Rejections-35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The DNA molecule, as claimed, has the same characteristics and utility as those found naturally in the genome or as cellular precursors thereof and therefore does not constitute patentable subject matter. See *American Wood v. Fiber disintegrating Co.*, 90 U.S. 566 (1974), *American Fruit Growers v. Brogdex Co.*, 283 U.S. 2 (1931), *Funk Brothers Seed Co. V. Kalo Inoculant Co.*, 33 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 91980).

Amendment of the claims to change "An aldehyde oxidase" to -- An isolated aldehyde oxidase--would overcome the rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1st Paragraph

Claims 1-3, and 8-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for isolation of the aldehyde oxidase gene from maize plant (Zea mays L.) which were identified by SEQ ID 1, 2, 3 and 4, does not reasonably provide enablement for the isolation of this gene from other plants and microorganisms.

The breadth of the claims are not commensurate in scope with support for enablement set forth. Applicants claim any aldehyde oxidase gene isolated from any plant and microorganisms. Applicants provide no other examples for the isolation and sequencing any other nucleotide sequence which encodes other aldehyde oxidase with the exception of those identified in SEQ ID 1, 2, 3 and 4. Applicants disclosed in the specification only the isolation of the aldehyde oxidase gene from maize plant (Zea mays L.) which were identified by SEQ ID 1, 2, 3 and 4. Taken together, the instant disclosure lacks the proper and sufficient guidance to enable the claims as set forth. Applicant's disclosure does not provide sufficient representative examples for identifying

and sequencing the nucleotide sequence(s) for other aldehyde oxidase gene from maize, or any other plants and microorganisms.

In view of the breadth of the claims, unpredictability, lack of guidance in the specification of the results as stated above, it is the examiner' position that one skilled in the art to which it pertains, or with which it is most nearly connected, could not practice the invention commensurate in scope with these claims without undue experimentations. See *In re Bell*, 26 USPQ2d 1529, 1532 (Fed.Cir. 1993) and *In re Deuel*, 34USPQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ 2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene (or promoter) is not reduced to practice until the inventor can define it by " its physical or chemical properties" (e.g., DNA sequence), and at page 1027, where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof. See *Genentech, Inc. v. Novo Nordisk*, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. See also *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the

description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for production of transgenic tobacco, carrot, pea and alfalfa , does not reasonably provide enablement for obtaining transformants with this gene from any other plant species and microorganisms.

The breadth of the claims are not commensurate in scope with support for enablement set forth. Applicants claim the transformation of the aldehyde oxidase gene into any host cell including those of other plant species and organisms. Taken together, the instant disclosure lacks the proper and sufficient guidance to enable the claims as set forth. Applicant's disclosure does not provide sufficient representative examples for obtaining transformants with aldehyde oxidase gene from any other plant species and microorganisms. Furthermore, the instant disclosure does not disclose any information to determine if these transgenic plants contain an elevated level aldehyde oxidase activity. This is important in the light of the fact that expression of foreign genes in transgenic plants is unpredictable, as shown by the teaching of Matzke and Matzke (Plant Physiology. 1995. 107: 679-685) that transgenes often become methylated in both plant and animal cells (Plant Physiology. 1995. 107: 679-685) in page 68, lines 14 to 19. Matzke and Matzke teach that transgenes are recognized as "foreign" by a genomic immune function (page

681, lines 18 to 19). Matzke and Matzke termed this type of gene silencing as co-suppression or sense-suppression which involves the coordinate silencing of the transgene with the homologous endogenous gene. In a poll conducted with 30 companies, Finnegan and McElory reported that nearly all of them reported some problems with unwanted silencing of transgenes (Finnegan and McElory. 1994. Transgene inactivation: plants fight back. Bio/Technology. 12: 883-888). Furthermore, the process of transforming plants with individual genes to obtain desired phenotypes is unpredictable. Napoli et al. observed a reversible inhibition of expression of the desired gene, when introduced in sense orientation into a plant, so that the desired phenotype was not observed (see page 279, Abstract). In addition, the introduction of single genes which encode a single enzyme in a metabolic pathway may be insufficient to effect the desired phenotype in the transformed plants, due to feedback inhibition, improper levels of various substrates or precursors, or the influence of other factors on the phenotype.

Carvalho et al. teach that expression of the resistant gene glucanase in transgenic plants was silenced in a homozygous transgenic tobacco line (T17). Carvalho et al. further teach that transgenic glucanase mRNA was detected at high level in the homozygous plant during the first 4 weeks of development. Carvalho et al. further teach that after 4 weeks, the mRNA level decreased gradually. In some Nicotiana sylvestris plants transformed with a p35S-chitinase gene the lower leaves showed a high chitinase content, whereas the upper leaves, formed later in development, showed low chitinase content and co-suppression of both the transgenic and the

endogenous chitinase gene (Carvalho et al. The EMBO Journal. 1992. Vol. 11: 5995-2602. The 4th paragraph under the Discussion section).

Given the claim breadth, unpredictability, and the lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to optimize the condition of tissue culture and transformation of the aldehyde oxidase into other plant species and microorganisms.

Applicants' disclosure does not demonstrate any reliable procedure for optimization of gene expression in microorganisms. Expression of heterologous proteins in E. coli as is unpredictable as taught by Ejdeback et al. (Protein Expression and Purification. 1997. Vol. 11: 17-25). Ejdeback et al. teach the effects of codon usage and vector-host combinations on the expression of spinach plastocyanin in E.coli. Ejdeback et al. teach that expression of heterologous proteins in E. coli can be difficult because of the differences in codon usage between E. coli and the organism from which the gene was obtained, as common codons in the latter might be rare codons in the former. Ejdeback et al. teach that rare codons are translated more slowly and stretches of rare codons are believed to cause ribosomes to stall, causing premature termination and/or less frequent initiation of translation (page 17, last paragraph on the right). Ejdeback et al. teach that since the ribosome covers a region of at least nine codons, numerous rare codons within this distance are proposed to be effective in slowing down the ribosome movement and the following ribosomes on the same mRNA. Ejdeback et al. teach that slower translation may also permit formation of secondary structures acting as termination signals or nuclease-sensitive sites

on the mRNA. Altogether, this might result in a lower mRNA level and therefore a lower yield of the recombinant protein (page 18, first paragraph on the left) . Ejdeback et al. teach the usage of site-directed mutagenesis to introduce changes that affect both mRNA and protein stability in order increase the level of expression (page 18, lines 15-16).

Mehta et al. teach that differences in protein expression can be due to the use of preferred codons which is thought to be due to differences in tRNA pool. Mehta et al. teach that consistent with these observations, the cDNA (consisting of a large number of "nonpreferred" E. coli codons) encoding the hIL-5 protein was cloned into pET11a vector (plasmid for expression of T7 RNA polymerase), and insignificant amounts of protein were obtained upon induction with IPTG (page 87 lines 1-10 of paragraph 3 on the left. Protein Expression and Purification. 1997. Vol. 11: 86-94).

In view of the breadth of the claims, unpredictability, lack of guidance in the specification of the results as stated above, it is the examiner' position that one skilled in the art to which it pertains, or with which it is most nearly connected, could not practice the invention commensurate in scope with these claims without undue experimentations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-9 are rejected under 35 U.S.C 103 (a) as being unpatentable over Liu et al. (Proce. Natl. Acad. Sci. (USA) 1994. Vol. 91: 1888-1892) in view of Felsted et al. (The Journal of Biological Chemistry. 1973: Vol. 248: 2580-2587) and, Berger and Kimmel (Guide to Molecular Cloning Techniques. Method f Enzymology. Associated Press. 1987).

Liu et al. teach a reliable protocol for the production of transgenic tobacco and potato plants (abstract).

Liu et al. do not disclose the production of transgenic plants that overexpress aldehdye oxidase.

Felsted et al. discloses the purification of the aldehyde oxidase to homogeneity (Abstract).

Berger and Kimmel disclose detailed description of a procedures for the isolation of cDNA and genomic clones (pages 173-371).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to utilize the teaching of Liu et al. of production of transgenic tobacco and potato plants that express kanamycin resistance marker and osmotin gene, and to modify them by incorporating the teaching of Felsted et al. of aldehyde oxidase purification and of Berger and Kimmel relating to

screening libraries to obtain cDNA and genomic clones . Liu et al ., Felsted et al. and, Berger and Kimmel are combinable because they are from similar problem solving area, viz., production of transgenic plants with desirable traits. The motivation for doing so would have been to produce transgenic plants that have the ability to detoxify various xenobiotic and increase the level of tolerance against various biotic stresses. . Therefore, it would have been obvious to combine Liu et al. with Felsted et al. and, Berger and Kimmel to obtain the invention as specified in claims 1-16.

Prima Facie -obviousness

It is the Examiner's position that all elements of Applicant's invention with respect to the specified claims are instantly disclosed or fully envisioned by the teaching of the references cited.

Conclusion

Claims 4-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Future Correspondence

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Ousama M-Faiz Zaghmout whose telephone number is (703) 308-3724. The Examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Douglas Robinson, can be reached on (703) 308-2897. The fax phone number for the group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to THE MATRIX CUSTOMER SERVICE CENTER whose telephone number is (703) 308-0196.

Ousama M-Faiz Zaghmout Ph.D.
March 8, 1998

DOUGLAS W. ROBINSON
SUPERVISORY PATENT EXAMINER
GROUP 1800